Treatment of Orthostatic Hypotension: Interaction of Pressor Drugs and Tilt Table Conditioning

Robert D. Hoeldtke, MD, PhD, Stephen T. Cavanaugh, BA, John D. Hughes, BA

ABSTRACT. Hoeldtke RD, Cavanaugh ST, Hughes JD: Treatment of orthostatic hypotension: interaction of pressor drugs and tilt table conditioning. Arch Phys Med Rehabil 69:895–898, 1988.

• We describe a patient with severe orthostatic hypotension in whom tilt table conditioning had a striking, beneficial effect. Upon presentation, the patient was unable even to sit, and the deconditioning associated with prolonged bed rest worsened his autonomic dysfunction. Although he was sensitive to the pressor effects of vasoconstrictor drugs (dihydroergotamine, caffeine, and a somatostatin analogue), these agents failed to stabilize his walking blood pressure. With drug therapy, however, the patient could maintain an adequate blood pressure while performing isometric exercises on a tilt table, whose angle was gradually increased during three weeks. After this conditioning program, pressor drug therapy made it possible for the patient to walk. Although the physiologic basis for this therapeutic response is unclear, our results indicate that tilt table conditioning may be an important adjunct to drug therapy in patients with severe orthostatic hypotension.

KEY WORDS: Hypotension, controlled; Hypotension, orthostatic; Pressoreceptors

Prolonged bed rest or exposure to weightlessness can lead to deterioration in the cardiovascular adaptation to shifts in posture.[4,12] Although the physiologic basis for this deconditioning is poorly understood,[3] the orthostatic intolerance which follows prolonged bed rest can be prevented by having patients sleep on an oscillating bed.[16] Similarly, patients with spinal cord injuries or other debilitating illnesses which prevent standing must be reconditioned to the upright posture gradually[14]; this is commonly accomplished on a tilt table.[15] Little is known about the effects of physical conditioning on orthostatic intolerance which develops in patients with autonomic dysfunction, although several such patients have been reported to benefit from sleeping with the head of their bed elevated.[1,9] We describe a patient with severe autonomic neuropathy who had been unable to stand or sit for such a long time that the deconditioning associated with prolonged bed rest confounded the failure in reflex vasoconstriction. Three weeks of therapeutic conditioning on a tilt table, however, coupled with the use of pressor drugs, led to a dramatic improvement in his orthostatic hypotension.

CASE REPORT

A 54-year-old man had a six-year history of severe orthostatic hypotension. The patient was impotent but had no gastrointestinal complaints or other symptoms of autonomic dysfunction. Recurrent syncope caused him to stop working as a truck driver. The problem progressed to the point where he was unable to even sit without feeling dizzy and short of breath. During the year before his admission, he could walk only in a squatting position; eventually he could only crawl. Despite these precautions, he lost consciousness as much as three times a day. Therapy with fludrocortisone, propranolol, ephedrine, and indomethacin was ineffective.

The patient had no symptoms of Parkinsonism or other diseases of the central nervous system. He had no history of alcoholism and no symptoms of a peripheral neuropathy. There was no family history of autonomic dysfunction or other neurologic diseases.

The patient's supine blood pressure was 150/80; after one minute of sitting it was 70/40; on attempting to stand the patient lost consciousness almost immediately. His heart rate was fixed at 80 to 82 despite the hypotension. Otherwise, his general physical and neurologic examination was normal. The patient was not dehydrated and his stool was heme-negative. The patient's hemoglobin was 11.5g/dl; hematocrit was 34. An SMA 18, a chest x-ray, and an electrocardiogram were normal. Serum protein electrophoresis and immunoelectrophoresis were normal. Rectal biopsy revealed no evidence of amyloidosis. Serum cortisol was 13μg/dl and responded normally to an ACTH challenge (0.25mg). There was no beat-to-beat variation with deep breathing; the post-Valsalva bradycardia/tachycardia ratio was 1.0 (normal response greater than 1.1). The patient's plasma norepinephrine concentration was decreased (0.53nmol/l) and was unaffected by shifts in posture. The norepinephrine metabolite concentrations in blood and urine were low (table 1), indicative of a generalized deficit in norepinephrine production, characteristic of patients with idiopathic orthostatic hypotension.[6,8]

METHODS

After being admitted and tested at our hospital, the patient was given a weight-maintaining diet containing between 80 and 120meq sodium/day. Caffeine-containing beverages were not allowed. Blood pressure was measured electronically by an Acutorr Datascope.[a] Dihydroergotamine (10–13μg/kg) was administered subcutaneously two hours before breakfast.[5] Caffeine (250mg) was administered in pill form, 30 minutes before breakfast. The somatostatin analogue (SMS–201–995)[b]

From the Department of Medicine, Division of Endocrinology/Metabolism, and the General Clinical Research Center, Temple University School of Medicine, Philadelphia, PA.

This study was supported by NIH grants AM32249 and AG06481 from the National Institutes of Health, Bethesda, MD, and GCRC grant RR00349 from the General Clinical Research Center, Temple University, Philadelphia.

Submitted for publication August 20, 1987. Resubmitted in revised form February 12, 1988, and accepted March 14, 1988.

No commercial party having a direct or indirect interest in the subject matter has conferred or will confer a benefit upon the authors or upon any organization with which the authors are associated.

Reprint requests to Robert D. Hoeldtke, MD, PhD, Division of Endocrinology/Metabolism, Temple University Hospital, 3401 North Broad Street, Philadelphia, PA 19140.

Table 1: Norepinephrine Metabolite Profile*

	Plasma**		Urine***	
	Patient	Normal range	Patient	Normal range
Norepinephrine	0.53	.75-4.5	0.088	0.08-0.63
Normetanephrine	---	---	0.046	0.16-1.1
Dihydroxyphenylglycol	2.18	2.65-7.1	0.138	0.07-1.0
3-Methoxy-4-Hydroxyphenylglycol	12.6	14.4-29	1.60	1.90-5.1
Vanillylmandelic acid	22.2	19.7-74	5.39	5.30-14.8

*Samples were collected with subjects fasting and supine.
**Plasma norepinephrinemetabolites are expressed nmol/l.
***Urinary metabolite excretion is expressed as nmol/m²/min.

was administered subcutaneously in doses ranging between 0.8 and 1.6μg/kg, either at the beginning or the end of breakfast.[7] Dihydroergotamine was always administered with caffeine.[5] The somatostatin analogue was given alone in some experiments, but was generally used in conjunction with dihydroergotamine-caffeine.

The experimental nature of our therapeutic program was explained to the patient and informed consent obtained. The studies were approved by the Institutional Review Board of our hospital.

Conditioning Program

The patient performed isometric exercises with his leg muscles twice a day for 45 to 60 minutes on a tilt table.[6] He was instructed to alternate between dorsiflexion and plantar flexion for ten cycles. After a brief rest (30sec), the cycle was repeated. Initially, the table was inclined at 30°; as the patient's orthostatic tolerance improved, the angle was gradually increased to 55°.[15] The exercise program was followed twice a day, seven days a week for three weeks.

Assessment of Therapeutic Response

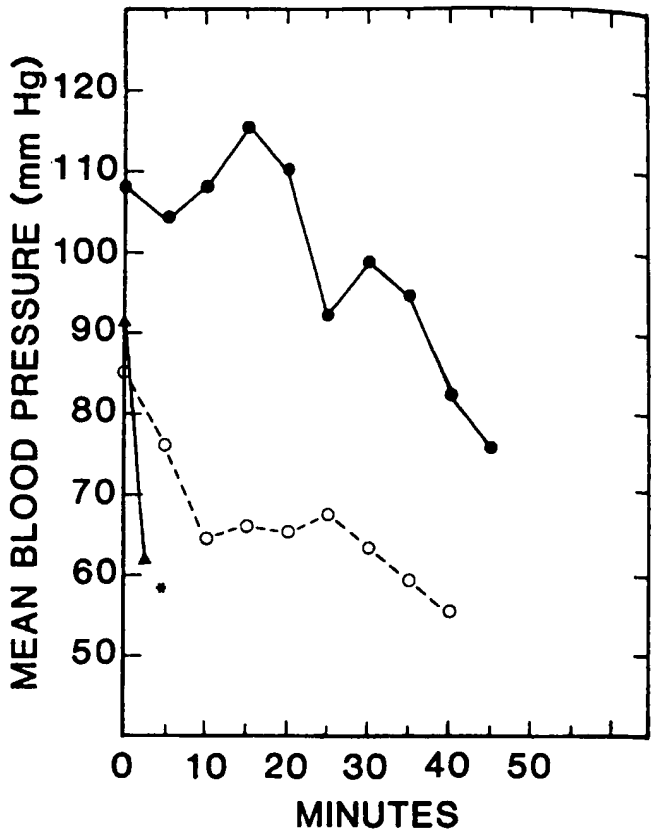
The patient was asked to stand and walk at the end of breakfast. His blood pressure was measured at 5-minute intervals, or more frequently if he appeared unstable. If presyncopal symptoms (shortness of breath, tingling in the feet, or dizziness) developed, the walking time was recorded and the experiment discontinued. Before initiating this protocol, we established by arterial catheterization and continuous blood pressure monitoring that these symptoms heralded incipient hypotension.

Chemical Methods

Plasma norepinephrine and dihydrophenylglycol were measured radioenzymatically.[11] Plasma and urinary norepinephrine metabolites were measured by high-pressure liquid chromatography using methods described elsewhere.[2,6]

RESULTS

During the initial week of hospitalization we observed that a moderate dose of either SMS-201-995 (0.4μg/kg) or dihydroergotamine (10μg/kg, in combination with 250mg caffeine) increased the patient's sitting blood pressure. Neither of these agents, however, alone or in combination, prevented the hypotension associated with standing. The patient fainted after walking one minute after large doses of both SMS-201-995 (1.6μg/kg) and dihydroergotamine (13μg/kg) were administered.



Effect of dihydroergotamine-caffeine and SMS-201-995 on orthostatic tolerance on a tilt table. ○—○ Indicates that the patient was administered SMS-201-995 (1.2μg/kg) ten minutes before adjusting the tilt table to 45°C. ▲–▲ Indicates that the patient was administered dihydroergotamine (13μg/kg) and caffeine (250mg) 120 and 30 minutes, respectively, before the tilt table. ●—● Indicates the combination of all three drugs, given in the same dosage and according to the same time schedule used when the drugs were given individually. The asterisk indicates that the patient fainted.

The tilt table conditioning program was initiated after it was evident that the pressor drugs failed to stabilize the patient's walking blood pressure. The patient became hypotensive, however, on the tilt table unless he was pretreated with dihydroergotamine-caffeine and SMS-201-995, as described above (fig 1). The pressor drugs would not maintain blood pressure on the tilt table unless the patient performed isometric exercises almost continuously. After three weeks of conditioning exercises the efficacy of the pressor agents first became evident (table 2); the patient was able to walk with a stable blood pressure for 24 minutes after the same drug program that had completely failed before conditioning. After a week of practice the patient was able to walk for 40 minutes. During the subsequent months the patient walked twice daily, and further improvement ensued. Now, one year after the tilt table conditioning, he can walk 90 or more minutes twice a day. The tilt table conditioning has not, however, led to a remission

Table 2: Effect of Tilt Table Conditioning on Walking Blood Pressure

		SMS-201-995 (1.6μg/kg)	Dihydroergotamine* (13μg/kg) and Caffeine** (250mg)	SMS-201-995*** Dihydroergotamine, and Caffeine
Before tilt table	Duration of walking (min)	1	1½	1
	Systolic BP after 1min walking (mmHg)	72†	75†	68‡
After tilt table	Duration of walking (min)	6	4	24
	Average systolic walking BP (mmHg)	93	80	100

*Dihydroergotamine was administered subcutaneously 2 hours before breakfast.
**Caffeine was administered orally 30min before breakfast.
***SMS-201-995 was injected subcutaneously at the beginning of breakfast.
†Indicates that the patient complained of shortness of breath and was unable to walk.
‡Indicates that the patient fainted.

in his underlying disease, and he remains unable to walk unless pretreated with both dihydroergotamine (10μg/kg) and SMS-201-995 (1.0μg/kg), three to five minutes before walking.

The patient has lost consciousness on this treatment program only twice during a year. In each instance this occurred in the morning before his daily injection. The drugs have left him free of adverse effects. The two-hour postprandial plasma glucose concentration has ranged between 150 and 190mg/dl.

DISCUSSION

This study demonstrates that a conditioning program on a tilt table was a critical aspect of the rehabilitation of a patient with autonomic neuropathy. Our findings are consistent with previous reports which have described patients with orthostatic hypotension who have benefited from sleeping with the head of their bed elevated.[1,9] Our treatment program incorporated isometric exercises that helped maintain the patient's blood pressure on the tilt table, which increased the magnitude of the postural stimulus (55° maximum) that we could use. Although this therapy led to an unequivocal beneficial effect, the physiologic basis for this therapeutic response is unclear. The cause of the orthostatic intolerance which follows prolonged bed rest or immobilization is poorly understood.[3,10] The plasma norepinephrine response to tilting is intact after prolonged bed rest, and the normal pressor response to infused norepinephrine and angiotensin II is maintained.[3] Tilt table conditioning had no effect, however, on the patient's plasma norepinephrine concentration. It is unlikely that a decrease in plasma volume during his prolonged bed rest[13] was a critical variable in the patient since he had been treated during this time with fludrocortisone (0.1mg/day) and there was no evidence of hemoconcentration at the time of his initial evaluation. We consider it unlikely that improvement in muscle strength during the exercise program was a critical factor in the reconditioning program. Exercise per se does not prevent the orthostatic intolerance associated with prolonged bed rest.[10] Although the isometric exercises probably improved the strength of his leg muscles, motor weakness was not evident before conditioning. The patient has muscular legs and was capable of supporting his weight. His inability to stand could be clearly attributed to symptoms of cerebral hypoperfusion. We suspect that the isometric leg exercises prevented pooling of blood in the feet and helped maintain the patient's blood pressure on the tilt table. This made it possible to gradually readapt the patient to the upright posture. The need for gradual readaptation to the upright posture is widely recognized in patients with other forms of orthostatic intolerance.[14,15]

CONCLUSION

A patient with severe orthostatic hypotension failed multiple therapeutic trials, experienced recurrent syncope, and became bedridden. A combination of potent vasoconstrictor drugs initially failed to stabilize his walking blood pressure, yet made it possible for him to perform isometric exercises on a tilt table. By combining pressor drug therapy[5,7] with tilt table conditioning, his orthostatic intolerance gradually improved and he regained the capacity to walk.

Acknowledgments: We thank Sandoz Pharmaceuticals for providing compound SMS-201-995 and dihydroergotamine; Dr. A.L. Tabuena of the Department of Physical Medicine and Rehabilitation, who assisted us with the conditioning program; and the nurses of the Temple University General Clinical Research Center, who took care of the patient and participated in these studies.

References

1. Bannister R, Ardill L, Fentem P: An assessment of various methods of treatment of idiopathic orthostatic hypotension. Q J Med **38**:377–395, 1969
2. Cavanaugh ST, Hughes JD Jr, Hoeldtke RD: Measurement of plasma vanillylmandelic acid by liquid chromatography with electrochemical detection. J Chromatogr **381**:13–19, 1986
3. Chobanian AV, Lille RD, Tercyak A, Blevins P: Metabolic and hemodynamic effects of prolonged bed rest in normal subjects. Circulation **49**:551–559, 1974
4. Deitrick JE, Whedon GD, Shorr E, Toscani V, Davis VB: Ef-

fects of immobilization upon various metabolic and physiologic functions of normal men. Am J Med 4:3–36, 1948
5. Hoeldtke RD, Cavanaugh ST, Hughes JD, Polansky M: Treatment of orthostatic hypotension with dihydroergotamine and caffeine. Ann Intern Med 105:168–173, 1986
6. Hoeldtke RD, Cilmi KM, Reichard GA Jr, Boden G, Owen OE: Assessment of norepinephrine secretion and production. J Lab Clin Med 101:772–782, 1983
7. Hoeldtke RD, O'Dorisio TM, Boden G: Treatment of autonomic neuropathy with a somatostatin analogue SMS-201-995. Lancet 2:602–605, 1986
8. Kopin IJ, Polinsky RJ, Oliver JA, Oddershede IR, Ebert MH: Urinary catecholamine metabolites distinguish different types of sympathetic neuronal dysfunction in patients with orthostatic hypotension. J Clin Endocrinol Metab 57:632–637, 1983
9. MacLean AR, Allen EV: Orthostatic hypotension and orthostatic tachycardia: treatment with "head-up" bed. JAMA 115:2162–2167, 1940
10. Miller PB, Johnson RL, Lamb LE: Effect of moderate physical exercise during four weeks of bed rest on circulatory functions in man. Aerospace Med 36:1077–1082, 1965
11. Passon FG, Peuler SD: A simplified radiometric assay for plasma norepinephrine and epinephrine. Anal Biochem 51:618–631, 1973
12. Piemme TE: Body fluid volume and renal relationships to gravity *In* McCally M (ed): Hydrodynamics and Hypogravics. New York, Academic Press, 1968, pp 133–161
13. Taylor HL, Erickson L, Henschel A, Keys A: Effect of bed rest on blood volume of normal young men. Am J Physiol 144:227–232, 1945
14. Taylor HL, Henschel A, Brozek J, Keys A: Effects of bed rest on cardiovascular function and work performance. J Appl Physiol 2:223–239, 1949
15. Vallbona C: Bodily responses to immobilization. *In* Kottke FJ, Stillwell GK, Lehmann JF (eds): Krusen's Handbook of Physical Medicine and Rehabilitation. Philadelphia, WB Saunders, 1982, pp 963–976
16. Whedon GD, Deitrick JE, Shorr E, Toscani V, Davis B, Stevens E: Modification of effects of immobilization upon metabolic and physiologic functions of normal men by use of an oscillating bed. Am J Med 6:684–711, 1949

Suppliers

a. Acutorr Datascope, Datascope Corporation, 580 Winters Avenue, P.O. Box 5, Paramus, NJ 07653–0005
b. Sandoz, Inc., Pharmaceutical Division, East Hanover, NJ 07936
c. LaBerne Manufacturing Company, Columbia, SC 29418

BOOK REVIEWS

REHABILITATION OF THE PHYSICALLY DISABLED ADULT, edited by C. John Goodwill and M. Anne Chamberlain. Softcover. 881 pages. $45.00. Published 1988. Sheridan Medical Books, Dobbs Ferry, NY.

This text is comprised of 51 chapters, each of which addresses a specific set of problems typically encountered in the rehabilitation process. Organizationally the book is divided into eight sections; the first focuses on generic issues associated with social, psychological and epidemiological goals of rehabilitation practice; the next four sections consider the rehabilitation process through the discussion of rehabilitation interventions specific to various diseases and disorders; the following section describes the phenomenon of rehabilitation by considering roles and functions of various team members; the next section reviews equipment needs and options available to persons requiring assistive devices; and the eighth and final section presents information about public and private organizations created to assist persons with disabilities. A brief discussion about the importance of research and development in rehabilitation is also found in this section.

The text has two major deficiencies as well as one considerable strength. The first deficiency is related to the breadth of topical issues presented. While the editors have attempted to bring together a wide variety of subject matter in a compendium-like fashion, what results is a series of chapters which do not blend well together. Some chapters are very practice-oriented while others are theoretical in nature. This lack of continuity between chapters tends to fragment and fractionate the total presentation of the subject matter. Further, because the text is not designed for a specific set of practitioners (ie, physicians, nurses, psychologists, etc.), but rather is written for all members of the rehabilitation team, its focus is further diluted.

A second deficit of this text is common to multi-authored, edited texts. The writing skills and knowledge base of contributing authors varies and further contributes to a less than optimal flow. A third, relatively modest problem with this text is that it was prepared by and for a British audience. Hence, the information presented in several chapters, particularly those outlining resource options, only is of interest and relevance to the British reader.

The text does have a rather notable strength in that it does attempt, and to some extent succeeds, to bring together in a single volume an enormous amount of information which is relevant to the uninitiated newcomer to the field. As such, it does provide a good overview of the complexity of issues and problems attendant to the rehabilitation process. (*M. G. Eisenberg, PhD*)

OCCUPATIONAL THERAPY WITH THE ELDERLY by Marjorie Helm. Soft cover. Price $22.00. 271 pages. Published 1987. Churchill Livingstone, Inc., 1560 Broadway, New York, NY 10036

This multiauthored book was written mainly *by* occupational therapists *for* occupational therapists with some chapters appropriately authored by a social worker, a dietician, a speech therapist, a chiropodist (Am. podiatrist), two solicitors (Am. lawyers) and two physicians.

Judging by the listing of the contributors and their respective professional appointments, the authors appear to be well qualified in their fields and this impression is fully substantiated when reading the text. Each chapter is appended by a vast literature reference and some list additional reading material. All this makes the book a very learned text.

In spite of the multiple authorship, there is hardly any repetition in the various chapters; these range from theories of aging through evaluating and treating the most often seen diseases and disabilities of aging persons (including self-care and other rehabilitative methods) to death and dying.

There is nothing really new in the book, but the complete coverage of the subject makes it virtually a textbook. Throughout the chapters is woven the ethical approach towards the aging patients, the stress of maintaining their dignity and their rights to freedom of choice and privacy. Social governmental and private agencies which are helpful to patient and therapist are fully described. Although the English social agencies are more completely involved in the care of the aged than American agencies, there is enough similarity for comparing these two countries.

Teamwork amongst health professionals is stressed as well as a holistic approach. Understandably, in this book the occupational therapists carries the major responsibilities for the entire rehabilitation program, but the activities of physical therapists, speech therapists, dieticians, podiatrists and social workers are fully covered. Physicians involved are mainly geriatricians; physiatrists are not mentioned. Quite interesting are also the discussions on hospital care, nursing homes, home care and day centers.

This book is worthwhile reading for all therapists, occupational, physical and speech, as well as for social workers and others, especially when entering the field of geriatrics. Physicians who care for the elderly, but are not experienced in medical rehabilitation, would also find this book interesting. The stress of the humane and empathical approach towards the aged, even when their minds are suffering from many years of use, is a message to all. (*Fritz Friedland, MD*)